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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
KERR, KATHLEEN M

ART UNIT	PAPER NUMBER
1652	18

DATE MAILED: 04/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/697,186	YOKOYAMA ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *4-9* is/are withdrawn from consideration.

5)☒ Claim(s) *2,3 and 10-19* is/are allowed.

6)☒ Claim(s) *1 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-Final rejection (Paper No. 14, mailed on September 10, 2002), Applicants filed a response and amendment received on January 7, 2003 (Paper No. 16). Said amendment amended Claims 1-3 and added new claims 10-20. Thus, Claims 1-20 are pending in the instant Office action. Claims 4-9 are withdrawn from further consideration as non-elected inventions. Claims 1-3 and 10-20 will be examined herein.

Priority

2. As previously noted, the instant application is granted the benefit of priority for the foreign application 309616/1999 filed in Japan on October 29, 1999 as requested in the declaration. Receipt is acknowledged of the translation of the priority document filed along with the response; the claimed mutants are disclosed therein. Thus, an effective filing date of October 29, 1999 will be used when considering prior art in the instant Office action.

Drawings

3. The drawings filed on January 7, 2003 have been approved by the Draftsmen and are, therefore, entered as formal drawings acceptable for publication upon the identification of allowable subject matter.

Withdrawn - Objections to the Specification

4. Previous objection to the Abstract for not completely describing the disclosed subject matter is withdrawn by virtue of Applicants' amendment.

5. Previous objection to the specification for being confusing with respect to SEQ ID NOs: 12-20 is withdrawn by virtue of Applicants' amendment to Table 1, which amendment identifies these SEQ ID NOs in the description.

Withdrawn - Claim Objections

6. Previous objection of Claim 3 under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim, is withdrawn by virtue of Applicants' amendment of Claim 1, which clarifies the scope of the mutations intended in the parent claim include mutations other than those specifically listed in Claim 1.

Withdrawn - Claim Rejections - 35 U.S.C. § 112

7. Previous rejection of Claims 1 and 3 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the scope of Claim 1. Applicants have amended Claim 1 and have argued that the scope is intended to be Interpretation B (see previous Office action) that encompasses any kanamycin nucleotidyltransferase (KNT) having any one or more of the nine point mutations relative to SEQ ID NO:1 and optionally *any other mutations* in the sequence.

8. Previous rejection of Claims 1-3 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "improved thermostability" is withdrawn by virtue of Applicants' amendment.

Maintained - Claim Rejections - 35 U.S.C. § 112

9. Previous rejection of Claim 1 under 35 U.S.C. § 112, first paragraph, written description, is maintained. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue that the ten mutant KNT sequences with improved thermostability disclosed in the instant specification adequately define the genus claimed that includes any number of additional changes to SEQ ID NO:1 with the proviso that one of the noted point mutations is also included. The Examiner disagrees. The instant claims are drawn to a very particular genus having a particular enzyme activity AND a particular thermostability; the more specific the genus, the more description required to adequately describe all the features (structural and functional) of all the members of the genus. In the instant case, the ten point mutations required in Claim 1 would have to adequately indicate to one of skill in the art the structure of other members of the genus. While KNT activity is adequately described in view of the specification and the art, the particular nature of the structure (sequence) of thermostable mutants is not predictably described. In other words, by having ten random examples without any described rhyme or reason to said examples, one of skill in the art would be unable to predict the structure of other members of the claimed genus. The number of examples required is directly linked to the skill in the art and the size and characteristics of the genus claimed. Thus, no one number is "a guarantee" and description must be considered on a case-by-case basis.

Applicants also argue that the limitation of having one of the ten point mutations listed defines a common characteristic. This argument is not persuasive because the point mutation

alone does not define the structure of the claimed polypeptide. The instant rejection is, thus, maintained.

The previous rejection is reiterated below for completeness:

> "Claim 1 rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant rejection is based solely on Interpretation B above of the scope of Claim 1.
>
> The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.
>
> In the instant specification, kanamycin nucleotidyltransferases (KNTs) are described by way of *S. aureus* sequences, wherein the wild-type is SEQ ID NO:11 and a WT* (well known thermostable mutant) is SEQ ID NO:1. By virtue of Interpretation B above, any KNT having any structure is encompassed by the claimed scope. Such proteins are only described by limited functional characteristics, which do not include a rationale for thermostability; no structural relationship is described among other KNT species or is used in the claims. Thus, one of skill in the art would be unable to predict the structure of other members of this genus by virtue of the instant disclosure. Therefore, claims drawn to KNTs without any specific structure are not adequately described."

10. Previous rejection of Claim 1 under 35 U.S.C. § 112, first paragraph, scope of enablement, is maintained. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue that additional mutations in the hydrophobic core and/or the dimmer interface would not be predicted to affect the thermostability of the protein in view of the

specification. The Examiner fails to see how this showing enables one of skill in the art to produce a functional nucleotidyltransferase. The rejection, as reiterated below, focuses on the low (virtually nonexistent) sequence identity between the disclosed sequence of a functional enzyme and the scope of the claim. Moreover, the one mutation in the hydrophobic core out of 29 total is about 3% of the mutations found; with a 253 amino acid sequence, up to 8 amino acids in the hydrophobic core might be expected to have the same effect.

Applicants argue that not all the Wands factors were considered. On the contrary, all the Wands factors were considered by the Examiner. However, only a sufficient number of factors to form a *prima facie* case were presented in the rejection. All factors need not be addressed specifically in the Office action so long as a *prima facie* case can be presented without relying on all the factors.

Applicants argue that determining whether or not a particular polypeptide falls within the scope of the instant claims would be easy considering the disclosure. This argument is not found persuasive because all the polypeptide must be MADE as well as used to be fully enabled. The point of the rejection of record is that one of skill in the art would be unable to MAKE all the members of the genus without undue experimentation using the specification and the art as guides. The lack of predictability or direction to produce all the members of the claimed genus of mutant nucleotidyltransferases is the most convincing Wands factor.

The previous rejection is reiterated below for completeness:

> "Claim 1 is rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for kanamycin nucleotidyltransferases (KNTs) having the sequence of SEQ ID NO:1 with the exception of any one or more of the nine point mutations listed in Claim 1, does not reasonably provide enablement for KNTs having any sequence while retaining catalytic activity and improving thermostability. The specification does not enable any person skilled in the art to which

it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The instant rejection is based solely on Interpretation B above of the scope of Claim 1. The amount of experimentation required of one of skill in the art to make the claimed invention to the full extent of its scope is undue....

The instant specification presents no guidance or working examples of the production of KNTs that have such low sequence identity with respect to SEQ ID NO:1 and that have improved thermostability other than the random means of "directed evolution". The variety of structures within the scope of the claim is virtually boundless except for the point mutation limitation, which is unclear. The nature of the invention is such that the KNT is a functional protein useful in the degradation of kanamycin; and with such an unlimited deviation from a known sequence, the predictability of functionality becomes extremely low. Moreover, the cause-and-effect relationship between improved thermostability and linear, amino acid structure is described in the specification using random (unpredictable) mutagenesis methods – no link between structure and function is described. Such enormous breadth and unpredictability renders the instant claims not enabled to the full extent of their scope without undue experimentation."

Withdrawn - Claim Rejections - 35 U.S.C. § 102

11. Previous rejection of Claims 1-3 under 35 U.S.C. § 102(a) as being anticipated by Hoseki *et al.* is withdrawn by virtue of Applicants' filing a translation of the Japanese priority document. Said document discloses SEQ ID NOs: 2 and 3, as well as the other point mutations claimed, thus, Claims 1-3 and 10-20 are granted the effective filing date of October 29, 1999, which date removes Hoseki *et al.* as prior art under the statute.

12. Previous rejection of Claim 1 under 35 U.S.C. § 102(b) as being anticipated by Matsumura *et al.* is withdrawn by virtue of Applicants' amendment removing the Ala62Val mutation from the optional mutations in the genus of the claimed polypeptides. Moreover, the Examiner notes that new Claim 10 was considered for rejection under 35 U.S.C. § 103(a) in view of Matsumura *et al.*

Claim 10 is drawn to, for example, the wild-type sequence (SEQ ID NO:11) with mutations of D80Y, T130K, and A62V (wild-type* is SEQ ID NO:1 which is SEQ ID NO:11 + D80Y and T130K). While Matsumura *et al.* teach the particular usefulness of the D80Y and T130K mutations, they do not teach any *particular* reason to combine the A62V mutation taught in Figure 4 with the D80Y and T130K mutations taught as thermostable mutants. Incidentally, although the A62V mutation is an option considering the hydroxylamine mutagen in the teachings of Matsumura *et al.*, A62V was never produced as a single thermostable mutant or in any double thermostable. Thus, the lack of motivation to particular combine these three point mutations renders Claim 10 unobvious in view of Matsumura *et al.*

NEW REJECTIONS

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claim 20 is rejected under 35 U.S.C. § 112, first paragraph, new matter, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The phrase "contains 1 to 19 point mutations" is not supported in the specification. While SEQ ID NO:3 contains 19 mutations and other sequences cited in Table 1 contain 9, 10, 11, or 13 point mutations and other sequences in Table 2 contain 1, 2, 4, 8, or 9 point mutations, the range of 1 to 19 point mutations is not supported in the specification. In particular, no mutant having 3 point mutations is found in the specification as

originally filed. Applicants are required to cancel the new matter or to cite clear support (page and line number) for the amendment.

14. Claim 20 is rejected under 35 U.S.C. § 112, first paragraph, written description, for the reasons noted above for the rejection of Claim 1.

15. Claim 20 is rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, for the reasons noted above for the rejection of Claim 1.

Suggested Claim Language

16. The following is not a rejection, but is the Examiner's suggestion for more suitable claim language, particularly in view of the record of the instant case having some confusion about the number of point mutations allowed in SEQ ID NO:1 to meet the limitations of the claim. While the instant claim language meets the statutory threshold of clarity and precision, a more suitable expression of the claimed subject matter is suggested. Such suggestions are encouraged in M.P.E.P. § 2173.02.

For Claim 10, the following language is suggested:

---10. An isolated mutant kanamycin nucleotidyltransferase comprising the sequence of SEQ ID NO:1 modified by point mutations selected from the group consisting of:

Met57Leu
Ser94Pro
Ser203Pro
Asp206Val
His207Gln
Ser220Pro
Ile234Val
Thr238Ala
and combinations thereof,

wherein said nucleotidyltransferase has improved thermostability as compared to SEQ ID NO:1.

Summary of Pending Issues

17. The following is a summary of the issues pending in the instant application:

a) Non-elected claims 4-9 remain pending and must be cancelled.

b) Claim 20 stands rejected under 35 U.S.C. § 112, first paragraph, new matter.

c) Claims 1 and 20 stand rejected under 35 U.S.C. § 112, first paragraph, written description.

d) Claims 1 and 20 stand rejected under 35 U.S.C. § 112, first paragraph, scope of enablement.

Conclusion

18. Claims 2, 3, and 10-19 are allowed in the Office action; Claims 1 and 20 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R.

§ 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK
March 31, 2003